DMICC Meeting 2007

Current Challenges in the Treatment of T1DM

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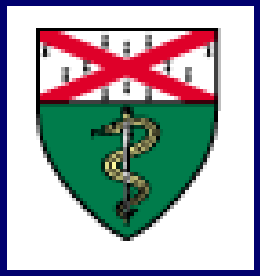


Focus

Better Treatment of Children and Adolescents with T1DM

- Most difficult to treat and are at highest risk for ultimate development of vascular and neuropathic complications of T1DM
- Need to do something now, not just a promise for the future

What We're Not Going to Cover

- Immune interventions to prevent T1DM or preserve beta cell function
- Islet transplantation

Because

- Established networks and projects are already addressing these areas
- Islet cell replacement therapies are not well suited for children with T1DM due to excessive morbidities related to immuno-suppression.

DCCT Results In Adolescents

192 of the 1441 patients were 13-17 years of age on entry (n=92 with Intensive Rx)

As in adults, intensive therapy reduced the risk of:

- Early Retinopathy
- Microalbuminuria

Even Greater Reduction in RR of Retinopthy Progression During EDIC

DCCT Recommendation
(J Pediatr,1994)

Most children and adolescents should be treated with intensive therapy to lower HbA1c levels as close to normal as possible.

EDIC addendum: and as early in the course of the disease as possible.

Special Challenges in Adolescents with T1DM

Compared with adults, intensively treated adolescents in the DCCT had:

- More Hyperglycemia (HbA1C 8.1 vs 7.1%) and
- 2X the risk of severe hypoglycemia
- Similar risk of excessive weight gain

Translation of DCCT Results into Practice

As feared, we've not done very well in youth with T1DM:

- A1c values remain far above ADA target of ≤ 7.5 %
- Severe hypoglycemic events occur all too frequently

Hvidore Study

- 21 Pediatric Diabetes Centers in 17 Countries (Europe, Japan and Canada)
- >2,700 Children and Adolescents with T1DM Enrolled
- Initial Study 1995 and Follow-up Study 1998

Hvidore Study Results

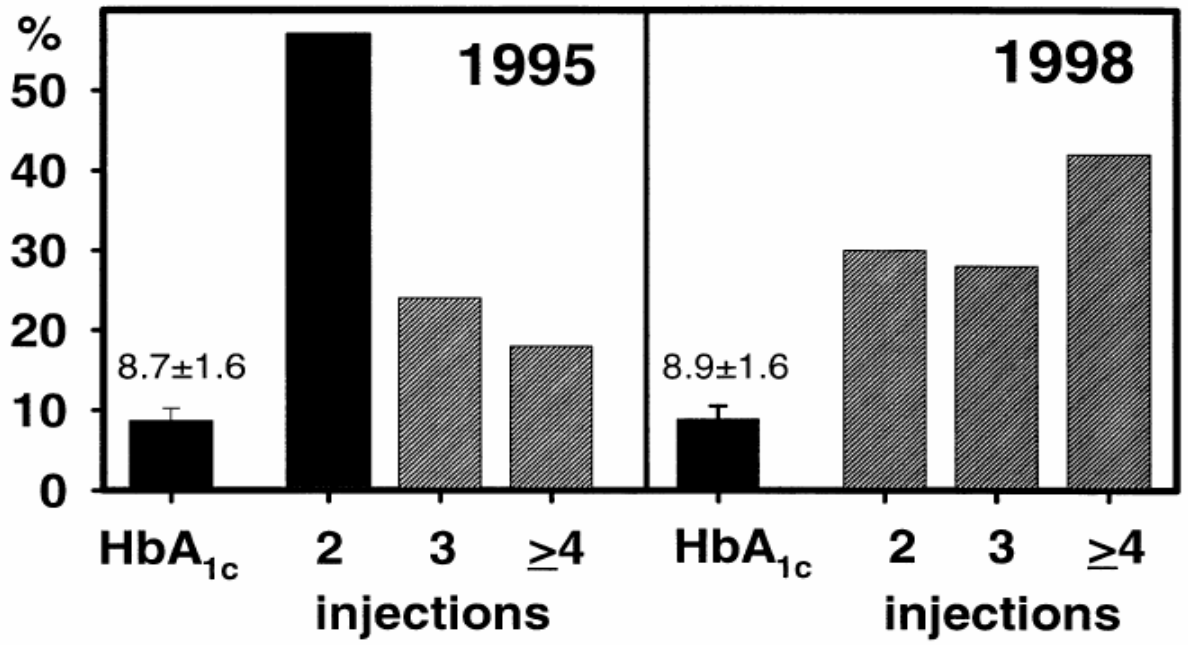


Fig. 2 Comparison of overall metabolic control as measured by mean HbA_{1c} (*solid bars*) and percentage of patients on 2, 3 and 4 or more injections (*shaded bars*) in 1995 (*left panel*) and 1998 (*right panel*)

Danne, et al., Diabetes Care 2001

Hvidore Study Results

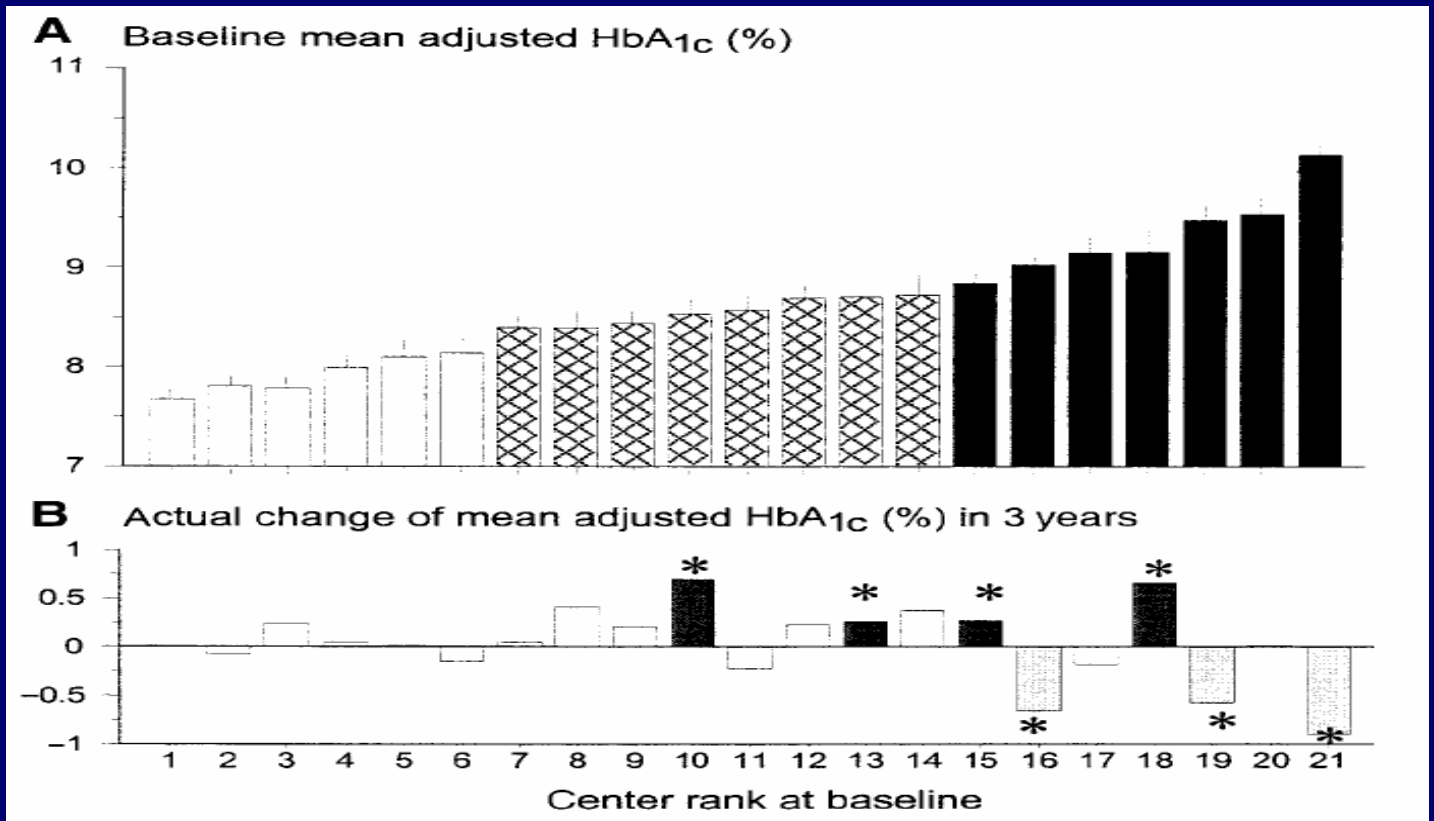


Figure 1—*Adjusted means ± SEM (adjustment for sex, age, and diabetes duration) of HbA_{1c} levels at participating centers at the baseline evaluation in 1995 (A). Centers with an HbA_{1c} level significantly below average (□), with average HbA_{1c} concentrations (▩), and with levels significantly above average are shown (■). The change in the adjusted mean after 3 years (B) is also shown. The three centers that significantly (*P < 0.05) improved their adjusted HbA_{1c} levels are shown with light gray bars, the four centers that significantly worsened are shown with dark gray bars, and those that had no significant change are shown with empty bars.*

Western Australia Population-Based Study

Fig. 2. Mean HbA1c and rates of severe hypoglycemia (coma/convulsion) in a large population-based sample of children and adolescents. Hypoglycemia rates increased as glycemic control improved with a plateau over the most recent period.

Treatment Advances Since the DCCT

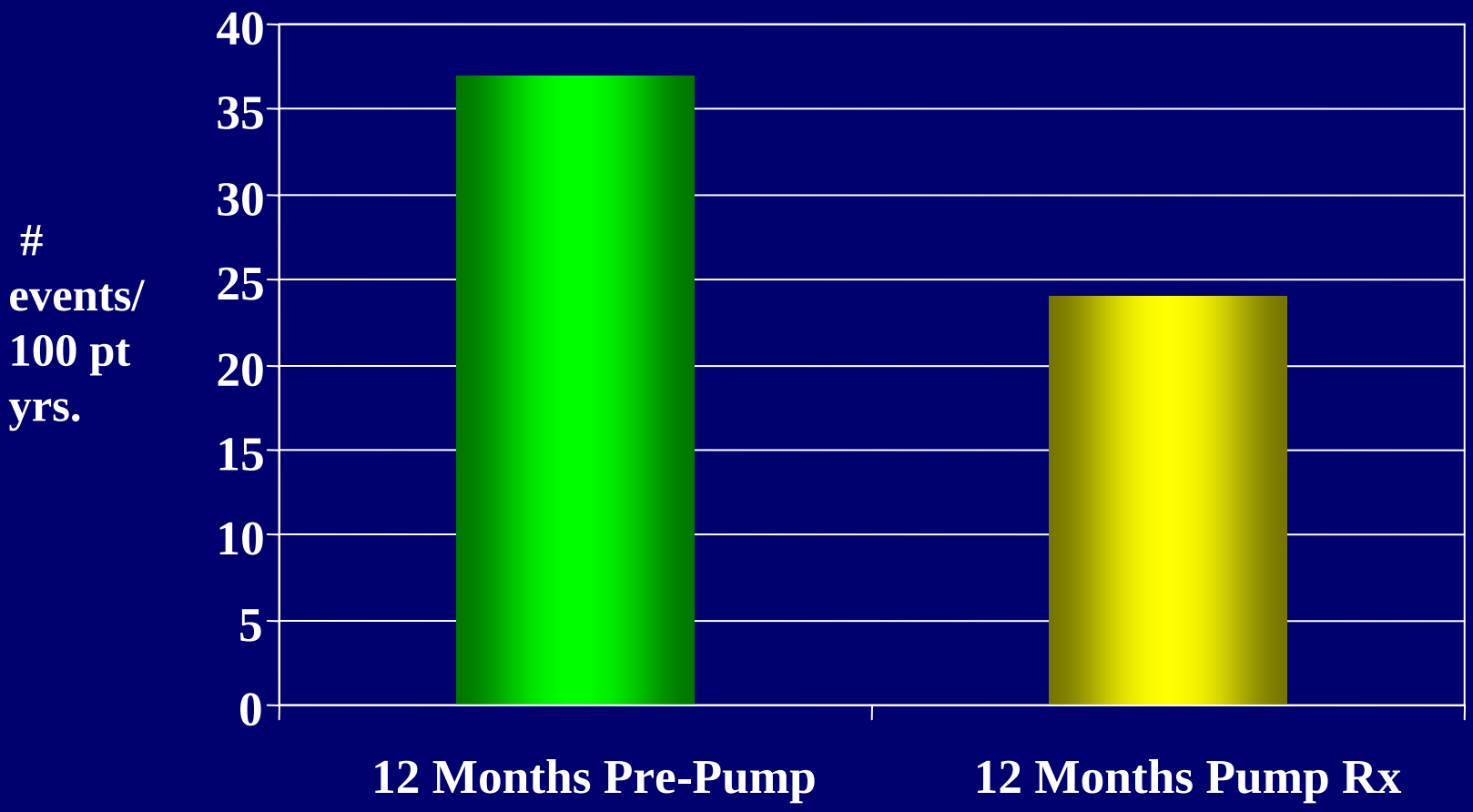
- Insulin Analogs
- Insulin Pumps

Non-randomized Pediatric Pump Studies (n=538)

Author	n	age (yrs)	A1c (%)
• Ahern	161	1-18	-0.7
• Maniatis	56	7-23	-0.3
• Plotnick	95	4-18	-0.4
• Sulli	40	4-25	-0.7
• Willi	51	5-17	-0.5
• Mack-Fogg	70	2-12	-0.5
• Weinzimer	65	1-6	-0.4

MEAN HbA1c 7.6%

Rates of Severe Hypoglycemia (seizure/coma) Too High



Ahern, et al. Ped Diabetes 2002

Real-time Continuous Glucose Monitoring Systems

Will the new systems for continuous glucose monitoring revolutionize Rx of T1DM?

WHEN will the new systems for continuous glucose monitoring revolutionize Rx of T1DM?

Potential benefits of CGM

- Open-loop Sensor Augmented CSII and MDI Therapy
- Closed-loop Insulin Delivery

Potential benefits of CGM in Open-loop Insulin Treatment

Improved Bolus Dosing

- –Trend arrows for real-time adjustments
- –Retrospective data to optimize C/I ratios and correction doses

Improved Overnight Control

- –Hypoglycemia alarms
- –Retrospective data to optimize overnight basal replacement doses

DirecNet

DIABETES RESEARCH IN CHILDREN NETWORK

- 5 clinical centers
  - Colorado
  - Iowa
  - Nemours
  - Stanford
  - Yale
- Coordinating center (Jaeb)
- Central laboratory (U Minn)

DirecNet Navigator Pilot Study of Sensor Augmented Pump Rx

- 30 insulin pump patients (4-17 yrs)
- Abbott Navigator glucose sensor used 24/7
- 3 month study
- Patients & parents use Navigator to adjust insulin doses in real-time and use sensor downloads for retrospective adjustments

DirecNet Navigator Pilot Study

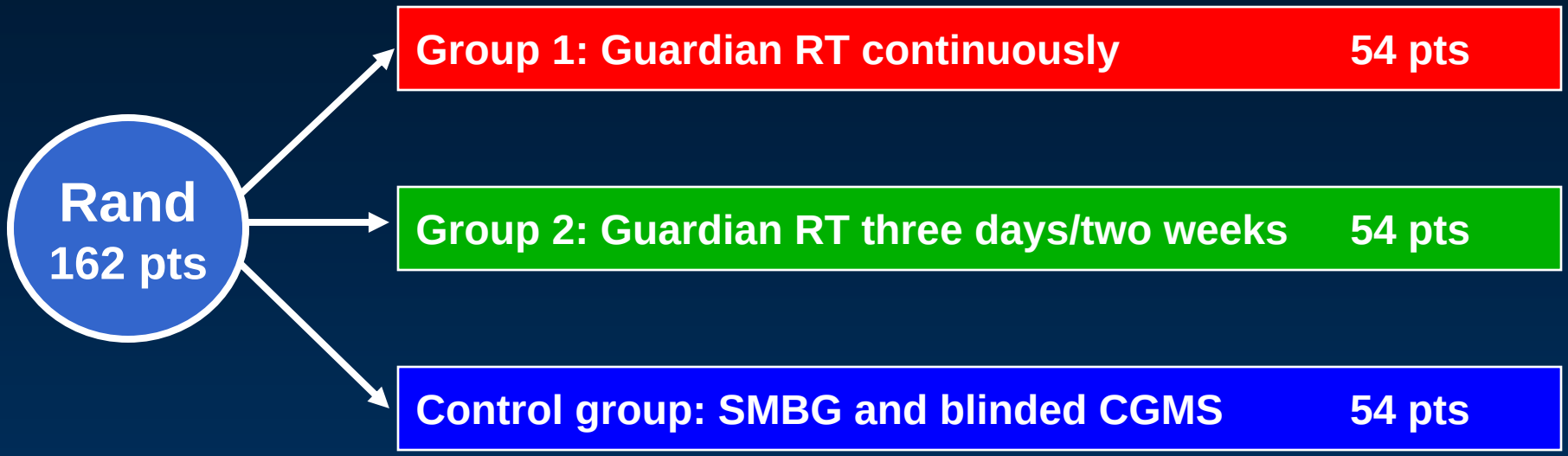
- **Accurate within 10-15% for up to 5 days**
- **Used ~130 hrs./wk**
- **Parents and patients very satisfied with device**
- **Improved metabolic control**
  - **A1c from 7.1 to 6.8%**
  - **↑ % of glucose values in target range**
  - **↓ Glucose variability (MAGE values)**

DirecNet Navigator Pilot Study

Red Flags?

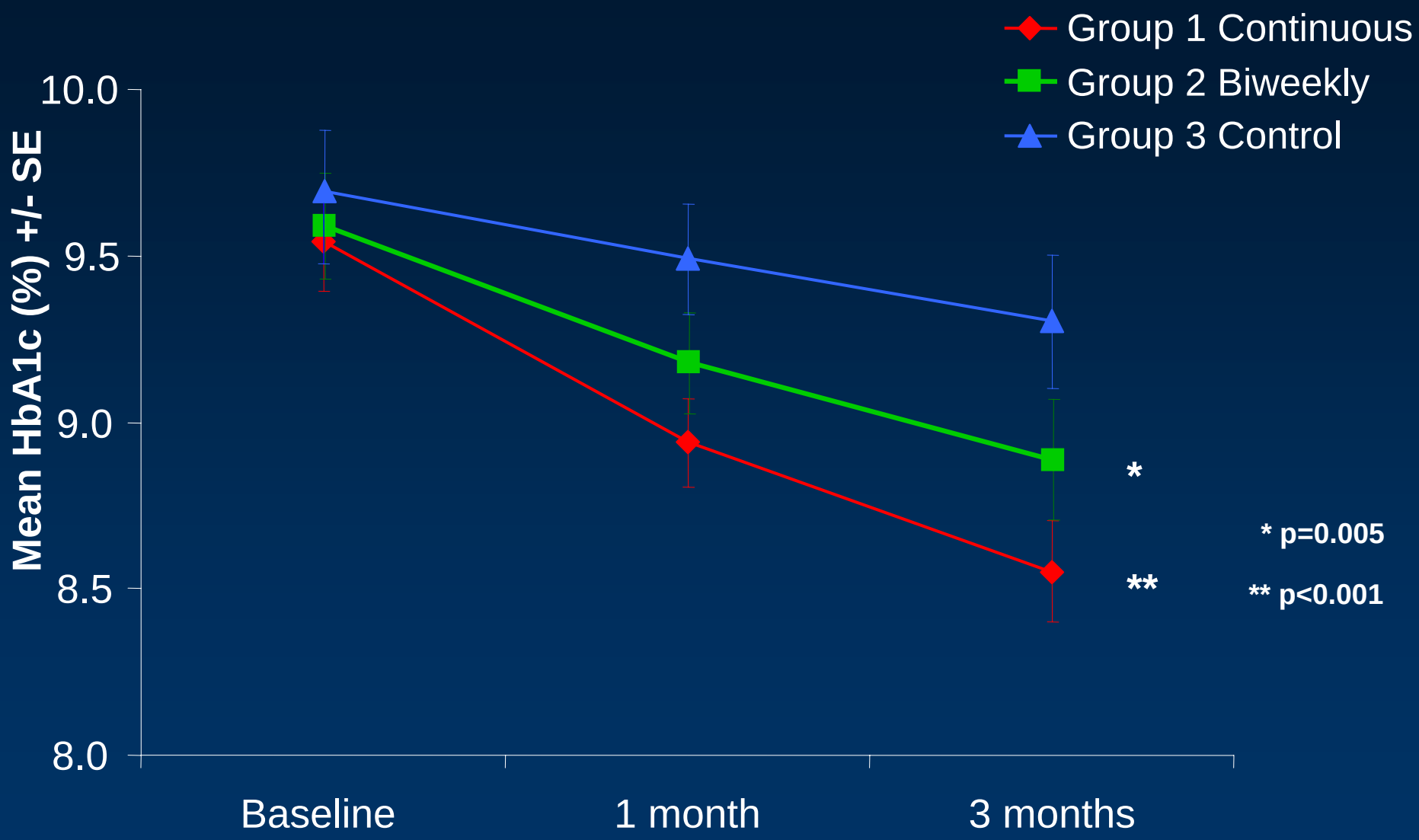
- **% of glucose values < 70 mg/d not decreased**
- **Reduced use of sensors during 14-26 week continuation phase in about 50% of the subjects**

Medtronic GuardControl Trial



- T1DM pediatric and adult patients (8-60yrs)
- HbA1c 8.1% or above
- CSII=78 and MDI=84

Results – HbA1c – Total population (n=162)

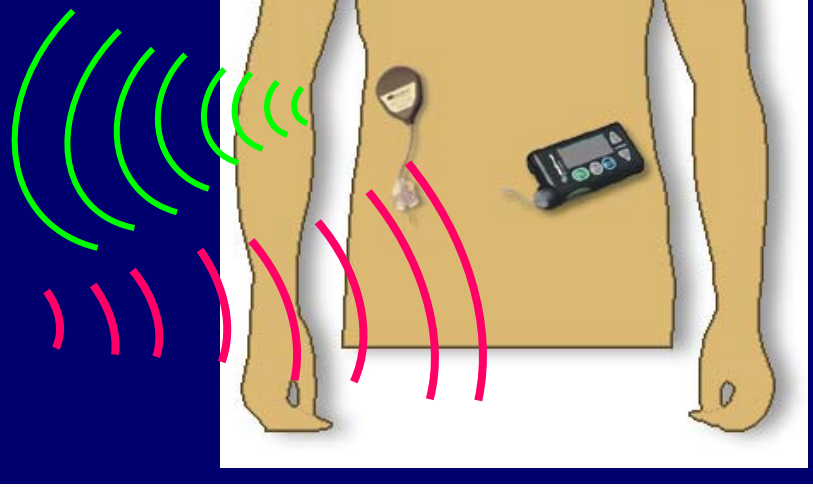


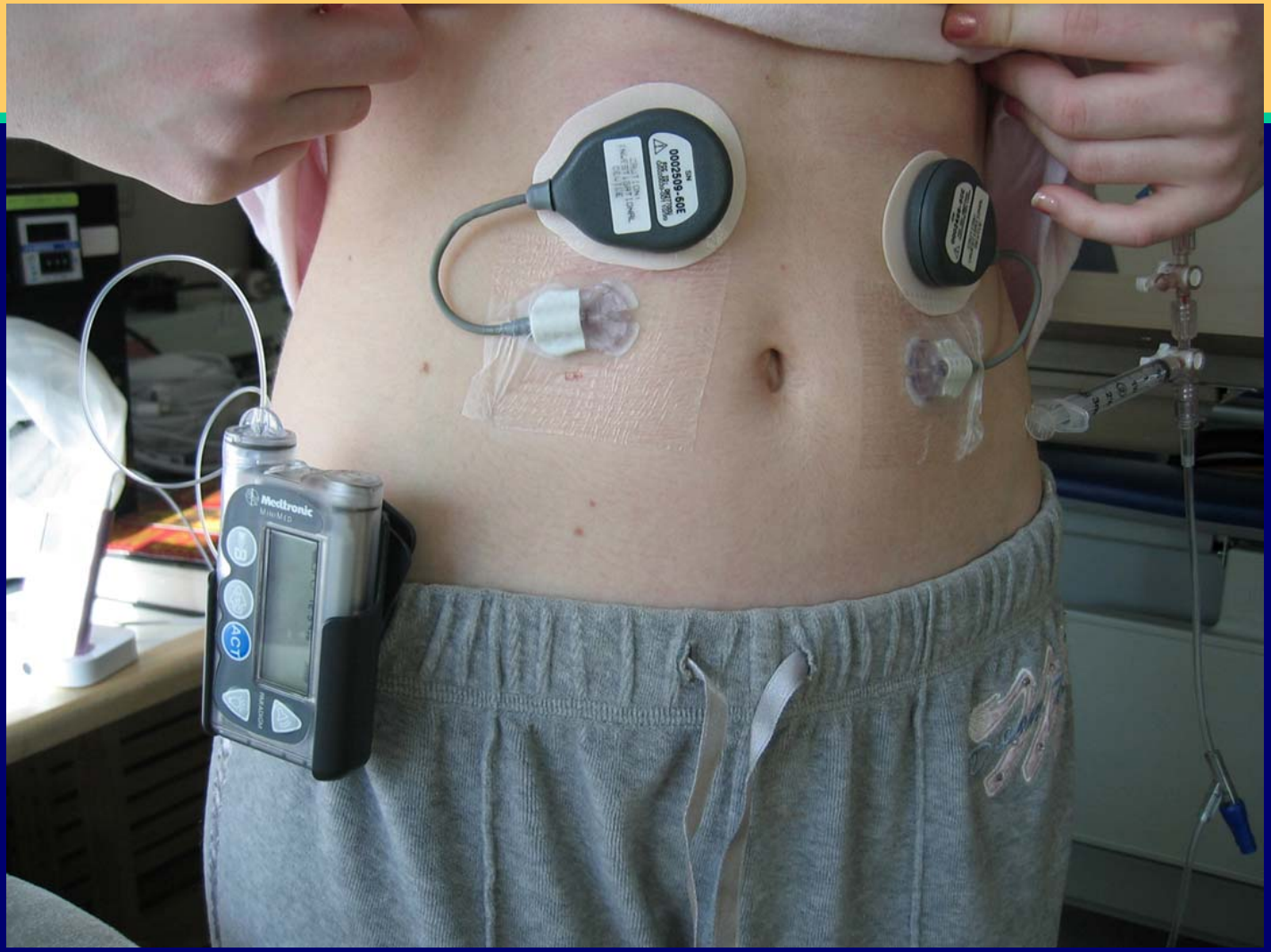
Ultimate reality

No treatment of diabetes will ever be perfect until there is feed-back control of insulin delivery that is regulated by fluctuations in plasma glucose

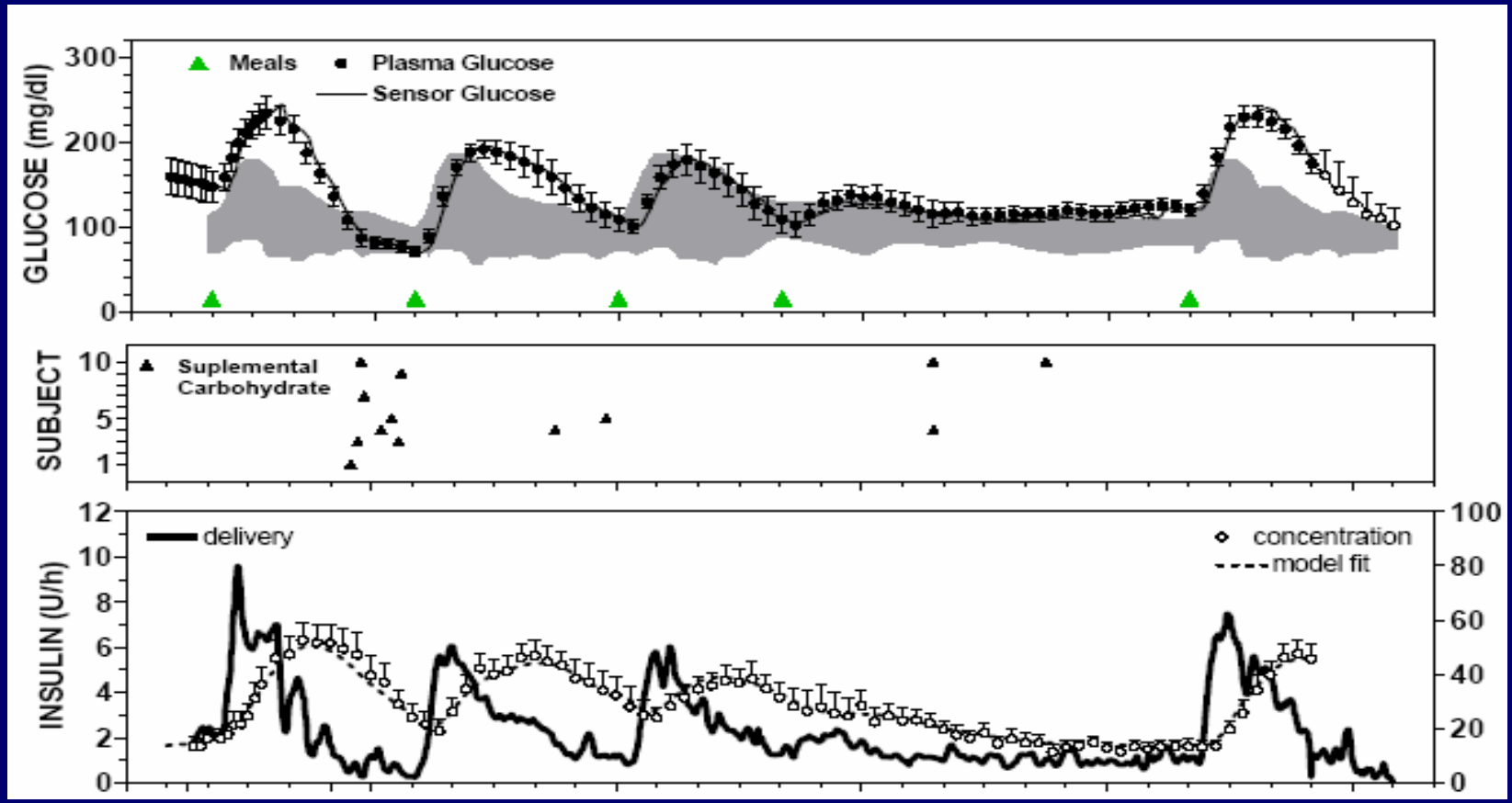
External Closed-loop Development System

- Sensor signals transmitted to a laptop computer that displays the sensor glucose and calculates rate of insulin delivery
- Rate of insulin delivery is transmitted to the insulin pump




Medtronic
MiniMed
ACT

Studies in Adults with T1DM (N=10)



Saad, et al., ADA 2004

Lessons Learned

Exaggerated post-meal excursions and a tendency to late post-prandial hypoglycemia due to lags in:

- Carbohydrate absorption
- Increases in interstitial glucose concentrations
- Insulin absorption from subcutaneous site

Excellent overnight control but lingering concerns re sensor accuracy

Possible Solutions

Exaggerated post-meal excursions:

- Hybrid, semi-automatic control with “priming” conventional pre-meal bolus to cover some of carbohydrate in meal

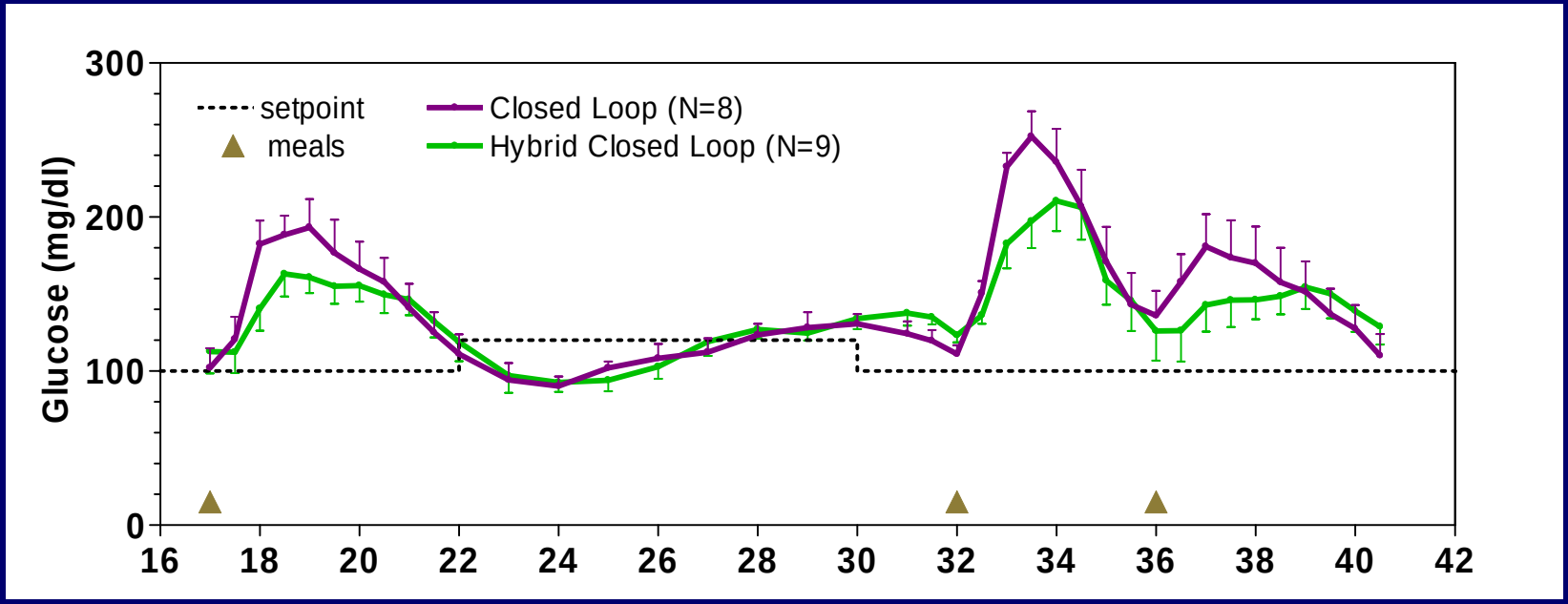
Sensor error

- Set slightly higher than normal target glucose value (e.g. 120 rather than 90 mg/dl) to avoid nocturnal hypoglycemia

Yale Full vs Hybrid Closed-Loop Study

- Subjects: 17 CSII treated adolescents with T1DM (9 full CL and 8 hybrid CL)
- Procedures: Closed-Loop control for 36 hours (6 AM Day 1 to 6 PM Day 2)
- Analyses: Plasma and sensor Glucose levels during last 24 hours

Mean Plasma Glucose Levels in 8 hybrid vs 9 full CL subjects



Preliminary Observations

- Short-term closed-loop control is feasible in children with T1D
- Night-time control is outstanding
- Meal-related excursions as good or better than traditional open-loop therapy and improved with manual priming bolus

Where do we go from here? Open-loop Use of CGM

Large-scale, relatively short-term (6-12 mos) RCTs to define the effects of CGM in CSII and MDI treatments on:

- A1c levels
- Behavioral and psychosocial outcomes
- Prevention of hypoglycemia

9 Center JDRF-sponsored study launched this week

Where do we go from here? Open-loop Use of CGM

Will use of CGM to reduce the frequency of hyper and/or hypoglycemia in very young children with T1DM have a beneficial effect on:

- Brain development
- Cognitive function

Can use of CGM help define the independent role of glucose variability on vascular complications of T1 or T2DM (oxidative stress hypothesis)?

Where do we go from here? Closed-loop Insulin Delivery

In-Patient Studies

- Test Improved insulin infusion algorithms
- Better control of meal-related glucose excursions
  - Effectiveness of titrating priming boluses
  - Adjunctive treatment with pramlintide or exenatide
- Better understanding of robustness of system under more “real-life” conditions
  - Exercise
  - Variable timing of meals
  - Multiple days of use

Where do we go from here? Closed-loop Insulin Delivery

Out-Patient Studies

- Night-time only
- 24 hour control

Where do we go from here?
Open and Closed-loop Use of CGM

Role of Industry: Develop devices that are

- Smaller
- More accurate

&

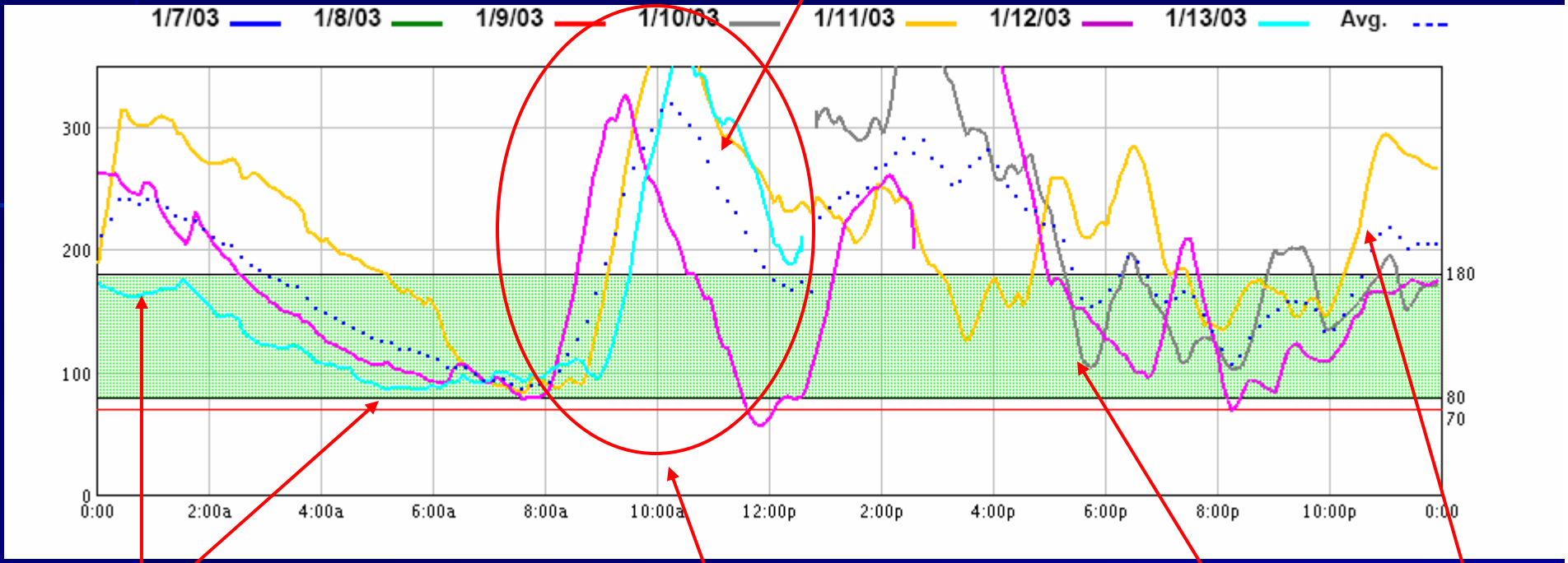
- Easier to Use

Margin of Error to Prevent Nocturnal Hypoglycemia

- Average Error of sensor ~14% when blood glucose between 80-180 mg/dl
- Set target sensor glucose at 120mg/dl

Sensor Glucose	Error	Actual Glucose
120 mg/dl	+33%	90 mg/dl
120 mg/dl	+50%	80 mg/dl
120 mg/dl	+100%	60 mg/dl

Average



Repeating Drop Overnight

Basal too high?
Correction dose?

Repeating post prandial rise then fall after breakfast

Check food-insulin factors

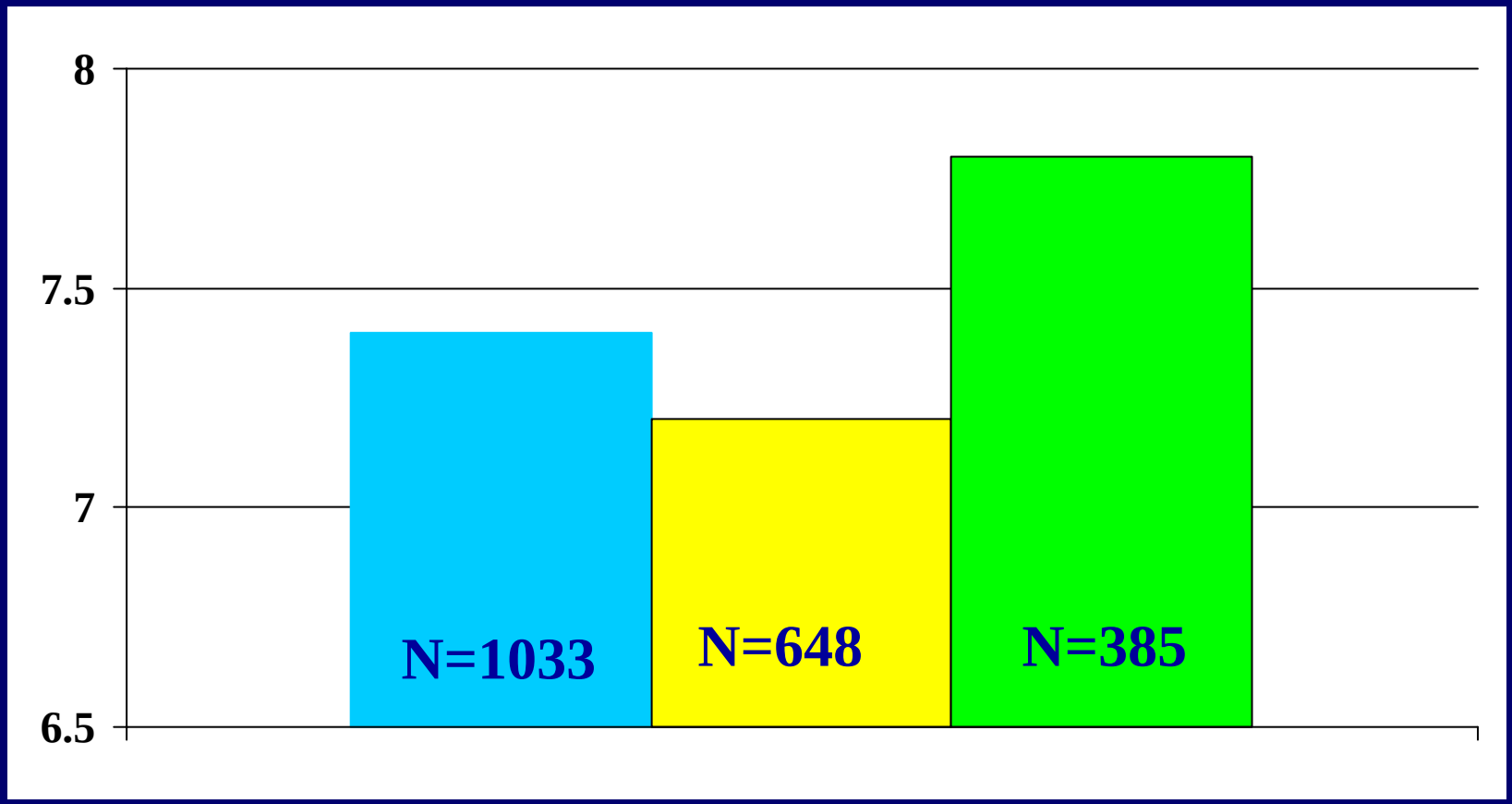
Rapid drops

Insulin correction?

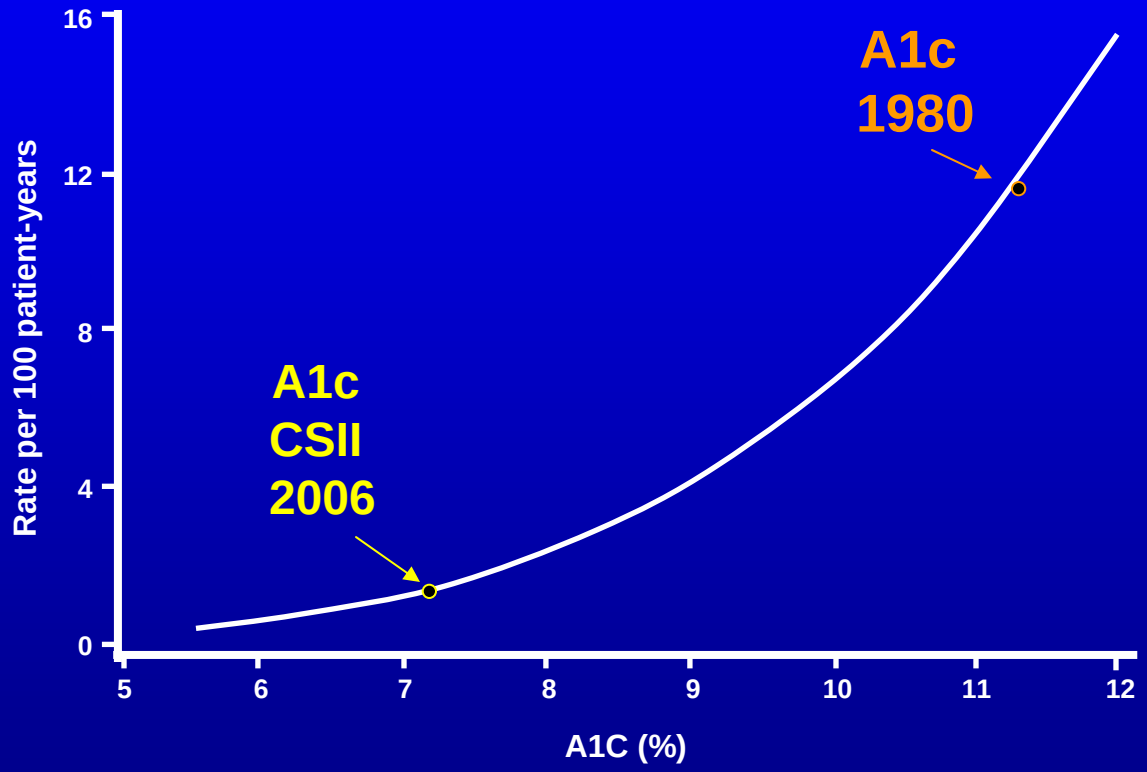
Bedtime snack

Sensor Daily Overlay

Clinic Wide Mean HbA1c Levels January, 2006



DCCT: Relationship of Microvascular Complications to Glycemic Control



Patients with Recent Eye Exam

(n=197)

Age Groups	Pre-screen (<10 yr)	Early Adolescent (10-14 yr)	Late Adolescent (14-18 yr)	Young Adult (18-22)
n	32	61	84	20
Duration of DM (yr)				
<3 yr	13	21	13	1
3 to 5 yr	9	15	14	5
>5 yr	10 (31)	25	57	14
HbA1c	6.6	7.3	7.5	7.9

n
130

% of Patients with Early Diabetic Retinopathy

0 %